

Renormalization of myoglobin-ligand binding energetics by quantum many-body effects

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We carry out a first-principles atomistic study of the electronic mechanisms of ligand binding and discrimination in the myoglobin protein. Electronic correlation effects are taken into account using one of the most advanced methods currently available, namely a linear-scaling density functional theory (DFT) approach wherein the treatment of localized iron 3d electrons is further refined using dynamical mean-field theory (DMFT). This combination of methods explicitly accounts for dynamical and multi-reference quantum physics, such as valence and spin fluctuations, of the 3d electrons, whilst treating a significant proportion of the protein (more than 1000 atoms) with density functional theory. The computed electronic structure of the myoglobin complexes and the nature of the Fe–O₂ bonding are validated against experimental spectroscopic observables. We elucidate and solve a long standing problem related to the quantum-mechanical description of the respiration process, namely that DFT calculations predict a strong imbalance between O₂ and CO binding, favoring the latter to an unphysically large extent. We show that the explicit inclusion of many body-effects induced by the Hund's coupling mechanism results in the correct prediction of similar binding energies for oxy- and carbonmonoxymyoglobin.

metalloprotein | strong correlation | optical absorption | quantum-mechanical simulation | natural bond orbitals

Significance Statement

Heme-based metalloproteins play a central role in respiration by transporting and storing oxygen, a function that is inhibited by carbon monoxide. Density-functional theory has been unable to provide a complete description of the binding of these ligands to hemes central iron atom, predicting an unrealistically high relative affinity for carbon monoxide. Here, we solve this problem using dynamical mean-field theory in combination with linear-scaling density-functional theory, thus allowing for a simultaneous description of crucial quantum entanglement and protein discrimination effects in the ground-state of the oxygen-heme complex. By simulating the binding process within a 1,000-atom quantum-mechanical model of the myoglobin metalloprotein, we obtain a significantly improved description of its spectroscopic and energetic observables.

Introduction

The ability of metalloporphyrins to bind small ligands is of great interest in the field of biochemistry. One such example is the heme molecule, which reversibly binds diatomic ligands, such as oxygen (O₂) and carbon monoxide (CO), and plays a crucial role in human respiration. Heme is employed in myoglobin (Mb) and hemoglobin (Hb) proteins to store and transport O₂ in vertebrates. The heme group of Mb is packed within a predominantly α -helical secondary structure and is coordinated by a histidine residue (known as the proximal histidine) as the fifth ligand of the heme's central Fe ion.

Despite intensive studies [1, 2, 3, 4, 5, 6], the nature of the bonding of O₂ to the iron binding site of the heme molecule

remains poorly understood, mainly due to the strong electronic correlation effects associated with its localized Fe 3d electrons. It is known that these electrons are energetically well-aligned with the π^* acceptor orbitals of CO and O₂, and that the molecules' bound conformations seek to maximize intermolecular orbital overlap [7, 8, 9]. In the case of MbO₂, the short Fe–O bond (1.81 Å [9]) implies that σ -bonding is supplemented, to some extent, by π -bonding [8]. Indeed, calculations employing the *ab initio* complete active space self-consistent method, in combination with a molecular mechanics force field to describe the protein (CASSCF/MM) [4], have identified a weak π -bonding mechanism in the Fe–O₂ bond that gives rise to an antiferromagnetic (open-shell singlet) state.

However, recent Fe L-edge X-ray absorption spectroscopy measurements on small biomimetic heme models lack the signature low-energy peak that is characteristic of the $d\pi$ hole, formed by metal-to-ligand charge transfer into the ligand π^* orbitals [10]. Although these spectroscopic results are more consistent with a strong Fe–O π interaction, some uncertainty remains about whether the same bonding picture holds in MbO₂, since the experiment was performed on a small model system (Fe(pfp)1-MeImO₂), which, in particular, neglects the distal histidine (His 64) that hydrogen bonds directly with O₂ in the protein.

Furthermore, while the diamagnetic nature of MbO₂ is well-established, there is little experimental evidence that directly addresses the extent of the charge transfer from Fe to O₂. Both CASSCF/MM [4] and L-edge X-ray absorption spectroscopy [10] suggest strong σ -donation from O₂ into the $d_{3z^2-r^2}$ orbital of iron (ligand-to-metal back charge transfer), which is hypothesized to limit the charge on the O₂ molecule to around $-0.5e$ [4]. However, the stretching frequency of the O–O bond in MbO₂ has been shown to be close to that of the free O₂[−] ion [11, 8], which motivates further study.

The energetics of diatomic ligand binding to the Mb protein are expected to depend strongly on the electronic structure of the heme site, and in particular on its orbital polarization. Specifically, Mb reduces the heme group's natural preference for CO binding: based on experimental equilibrium association constants, the binding free energy of CO,

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relative to O₂, is reduced from around 5.9 kcal/mol in a non-polar solvent to 1.9 kcal/mol in the protein environment [12]. The combination of the strong electronic correlation centered at the Fe binding site and long-ranged interactions between the protein and the charged O₂ molecule make computational modeling of the energetics of these complexes extremely challenging.

Typically, such studies calculate the protein effect [13, 14, 15], or relative spin state energies [16], or focus on small model systems [6]. However, most approaches applied to large system sizes did not include a proper treatment of electronic correlations. The effect of electronic correlations in the iron 3d states was investigated by some of us [13], where it was included, to an extent, in *ab initio* simulations of ligand discrimination in myoglobin via a DFT+*U* treatment. DFT+*U* has been shown to be an efficient method for correcting self-interaction errors in the approximate DFT description of transition-metal chemistry [19], and when combined with linear-scaling approaches [17, 18], it allows us to tackle such systems comprising thousands of atoms. It was found, in the case of Mb [13], that the protein discrimination effect is dominated by polar interactions between O₂ and the distal protein residue His64. However, a problem in the DFT+*U* calculations is that a strong residual energetic imbalance that favors CO over O₂ binding was observed [13], suggesting that approaches beyond static DFT+*U* are called for in order to obtain a proper description of myoglobin.

Recent progress has been made in the study of strongly-correlated electrons by means of dynamical mean-field theory (DMFT) [20], a sophisticated method that includes quantum dynamical effects, and takes into account both valence and spin fluctuations. DMFT is routinely used to describe materials, and recently has also been extended to nanoscopic systems [23, 24]. DMFT also explicitly includes the Hund's exchange coupling typically, although not always, neglected in DFT and DFT+*U* studies. DMFT was recently combined with linear-scaling DFT [21] to produce a linear-scaling DFT+DMFT approach [22]. By means of the latter, we have pointed out that strong correlation effects in heme are controlled by the Hund's coupling *J*, and not the Hubbard repulsion *U* alone [25], suggesting that subtle quantum many body effects are missing in the DFT+*U* treatment of myoglobin [13]. However, the computational model included just the heme group and diatomic ligands, neglecting entirely the protein environment and proximal histidine ligand, thereby strongly overestimating the binding energy of CO relative to O₂.

In the present work, we bridge state-of-the-art DMFT many-body calculations with large scale DFT calculations. We perform simulations of realistic models of the MbO₂ and MbCO complexes, comprising 1007 atoms, using linear-scaling DFT+DMFT. We thereby treat the electrostatic, steric, and hydrogen-bonding effects due to protein materials, together with the multi-reference, finite-temperature and explicit Hund's exchange coupling effects associated with the iron 3d binding site, in single, self-consistent calculations for the first time. We systematically investigate how the Hund's coupling alters the electronic structure at the heme site and, at the same time, corrects the long-simulated, unphysical imbalance between CO and O₂ binding affinities.

Results

We first discuss our results for the porphyrin-plane component of the optical absorption spectra of ligated myoglobin, computed using DFT+DMFT (Fig. 1), where a realistic value of the Hund's coupling *J* = 0.7 eV is considered (results obtained for *J* = 0 eV are shown for comparison). The absorp-

tion spectrum of this protein has been reported experimentally to be qualitatively dependent on its ligation state, in that a peak is present in the infrared region in the MbO₂ case but not for MbCO [26]. Our theoretical absorption spectrum is in good agreement with the experimental data obtained from sperm whale MbO₂ single crystals [27], and reproduces an MbO₂ infrared absorption band at \approx 1.2 eV, observed experimentally at 1.3 eV [28]. Our calculations associate this feature with a charge transfer band generated by the hybridization of the Fe atom and the O₂ molecule, in particular transitions of occupied porphyrin π and iron *d* orbital states into empty O₂ (π^*) orbitals. In MbCO, due to the strong covalent bond, the porphyrin π and *d* hybridized orbitals are at a lower energy and, hence, there is no contribution to the infrared spectrum. The double peak structure in the optical transition obtained at $\omega \approx$ 1.9 eV and 2.2 eV is also very close to experiments, where they are obtained respectively at 2.1 and 2.3 eV [28, 27]. We attribute this feature to the porphyrin Q band (π to π^* absorptions) and to corresponding charge transfer excitations. We find a broad Soret band centered theoretically at \approx 2.75 eV, close to the experimental peak obtained at 2.95 eV [28, 27]. For MbO₂, the spectrum at *J* = 0 eV is qualitatively similar. However, Fig. 1 also reveals that a non-zero *J* is required to recover the experimentally observed double-peak structure of the MbCO Q band [27]. Analysis of the spectral weight below the Fermi level in MbCO reveals the source of this splitting. For *J* = 0 eV, the orbital character of the HOMO is almost degenerate between the three *t*_{2g} orbitals. However, for *J* = 0.7 eV, we observe a splitting of the spectral weight of the *d*_{xy} and the *d*_{xz,yz} orbitals of \approx 0.3 eV, thus recovering the expected splitting of the charge transfer Q band in the optical absorption spectrum.

In order to further understand the nature of the bonding in the MbO₂ complex, we have found it instructive to transform the atomic basis functions, used to expand the DFT+DMFT density-matrix (that is, the frequency-integrated Green's function), into a set of natural bond orbitals (NBOs) [29, 30, 31]. The transformation is constructed such that the resulting orbitals may be categorized into localized Lewis-type bonding and lone pair orbitals, as well as their anti-bonding and Rydberg counterparts, thus allowing a chemically-intuitive population analysis to be applied to the DFT+DMFT many-body wave-function. Fig. 2 shows the σ - and π -bonding many-body natural bond orbitals of the MbO₂ complex. We find, in particular, that an O₂ π^* NBO (Fig. 2a), which has an occupancy of 1.5 e, and an anti-bonding NBO formed between Fe and the proximal histidine, with occu-

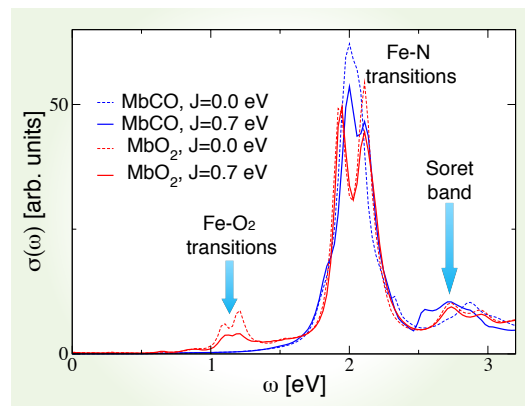


Fig. 1. Optics: porphyrin-plane component of the optical absorption spectrum calculated using DFT+DMFT, at *J* = 0 eV (dashed curves) and *J* = 0.7 eV (continuous curves), for MbCO (blue) and MbO₂ (red).

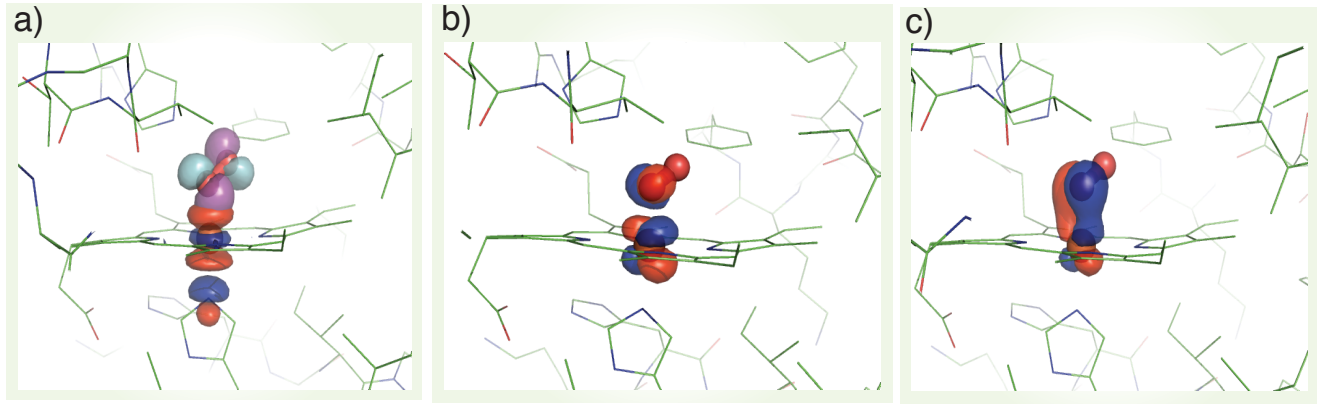


Fig. 2. Natural bond orbital (NBO) analysis of the DFT+DMFT Green's function for MbO₂: (a) An O₂ π^* type many-body NBO (cyan/magenta), of occupancy 1.5 e, which strongly-interacts (via the DFT Hamiltonian) with an anti-bonding Fe-based many-body NBO (red/blue), of occupancy 0.5 e. (b,c) many-body NBOs showing π -bonding between Fe and O₂; the NBO occupancies are 1.4 e and 1.8 e, respectively.

pancy 0.5 e and a strong $d_{3z^2-r^2}$ character, interact strongly via the DFT Hamiltonian. We note that the 0.5 e occupancy of the anti-bonding orbital on Fe is consistent with the ligand-metal back charge transfer process between O₂ and the Fe $d_{3z^2-r^2}$ orbital, which is observed both in CASSCF/MM [4], and with L-edge X-ray absorption spectroscopy [10]. Ligand-metal back charge transfer is also present at $J = 0$ eV, albeit with a smaller magnitude (0.34 e). Thus, electronic delocalization is expected to provide a greater energetic stabilization in the MbO₂ complex at $J = 0.7$ eV.

The net charge on the O₂ molecule, from natural population analysis, is -1.1 e, which is consistent with the Weiss picture of bonding in MbO₂ [2]. It is worth noting that state-of-the-art CASSCF/MM calculations point toward a smaller O₂ charge of -0.5 e [4]. Metal-to-ligand charge transfer is expected to occur *via* π -bonding interactions between Fe d orbitals and O₂ π^* [4, 10]. Indeed, Fig. 2b,c are characteristic of the multi-configurational CASSCF orbitals that make up the proposed π -type bonding in a previous study [4]. A notable difference between these calculations and the CASSCF/MM study is that the π -bonding is much stronger than previously reported. Here, 3.25 e are involved in π -bonding, as opposed to approximately 2 e in CASSCF/MM. Our calculations yield a $d\pi$ hole character of 19 %. This compares extremely favorably with recent Fe L-edge X-ray absorption spectroscopy measurements of a small biomimetic heme model, which estimates the $d\pi$ hole character to be 15 ± 5 % [10]. We, therefore, find that the π -bonding character in MbO₂ is similar to that in isolated porphyrins. We note that the stronger π -bonding interaction between the iron and O₂ also suggests that spin polarization of the π electrons is less likely [10], suggesting that a broken spin symmetry description of MbO₂ might not be entirely reliable.

Next, we show, in Table 2, a comparison of the computed Fe orbital density with and without the explicit inclusion of Hund's coupling J in the Hamiltonian. We find that the effect of J in MbO₂ is to bring the $d_{3z^2-r^2}$, d_{xy} , and $d_{x^2-y^2}$ orbitals

closer to single-electron occupation, so that the Hund's coupling enhances the spin magnetic moment on the Fe atom. Indeed, we find, in our calculations, a build up of a magnetic moment in the $d_{x^2-y^2}$, $d_{3z^2-r^2}$ and d_{xy} orbitals, with a concomitant electron occupation of $n \approx 1$ absent from our $J = 0$ eV calculation and from the CASSCF/MM approach. The latter discrepancy may be due to the fact that CASSCF does not include dynamical correlation effects and may also be dependent on the chosen active space. In MbCO, unlike MbO₂, we observe that the doublet on the d_{xy} orbital is not emptied as the Hund's coupling is increased. We next show, in Fig. 2a, the dependence of the Fe charge, computed using Mulliken analysis in the NGWF basis, on the Hund's coupling J for MbO₂ and MbCO, respectively. For MbO₂, we find that the charge of the Fe is transferred to the porphyrin ring and protein as the Hund's coupling is increased. In contrast, for MbCO we find a very weak dependence of the Fe charge on the Hund's coupling parameter (see Table 2). In our view, the latter indicates a very strong Fe-CO covalent bond, which remains stable against the Hund's coupling. We find that the charge transferred from the Fe to O₂ is 1.1 e at the physical value of the Hund's coupling $J = 0.7$ eV (see Fig. 2b), confirming the estimation obtained using natural population analysis.

Fig. 2 depicts the computed spin fluctuations in MbO₂ and MbCO, specifically, a histogram of the spin quantum number distribution obtained by looking at the 16 dominant

Protein	$d_{x^2-y^2}$	$d_{3z^2-r^2}$	d_{xy}	d_{xz}	d_{yz}
MbO ₂ ($J = 0.0$ eV)	0.82	0.38	1.99	1.90	1.92
MbO ₂ ($J = 0.7$ eV)	0.96	0.96	1.10	1.87	1.96
MbCO ($J = 0.0$ eV)	0.95	1.13	1.99	1.88	1.89
MbCO ($J = 0.7$ eV)	1.00	1.15	1.99	1.84	1.84
MbO ₂ (CASSCF/MM)	0.44	0.59	1.93	1.86	1.13

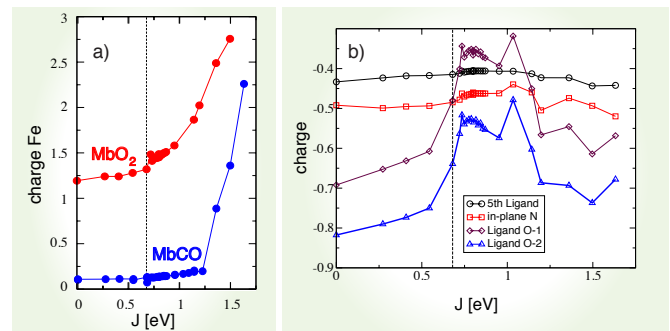


Fig. 3. Polarization: a) The dependence on J of the DFT+DMFT Mulliken charge of the Fe atom in MbO₂ and MbCO. b) Mulliken charges in MbO₂ of the two O atoms of O₂ (O-1 is bonded to Fe and O-2 forms a hydrogen bond with His 64). Also shown are the corresponding charges of the in-plane N atoms of the heme group and His93 (the 5th ligand of Fe).

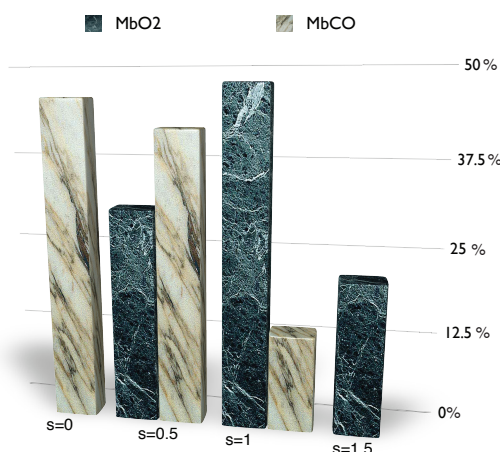


Fig. 4. Spin fluctuations: Spin-state distribution obtained by analyzing the 16 dominant states in the DFT+DMFT reduced density-matrix (see text) at $J = 0.7$ eV. The reduced density-matrix of MbCO has states with dominant $s = 0$ configurations, and MbO₂ has dominant contributions from $s = 1$, with higher spin contributions at $s = 1.5$.

states in the reduced ($3d$ subspace) density-matrix, obtained by tracing the atomic DMFT problem over the bath degrees of freedom. This gives an effective representation of the quantum states of the Fe atom. The ground-state wave-function is not a pure state with a single allowed value for the magnetic moment (singlet, doublet, triplet, etc.), yet we can describe the fluctuating magnetic moment of the Fe atom by analyzing the distribution of the magnetic moments obtained from the dominant configurations. In particular, we find that the reduced density-matrix of MbCO has states with dominant $s = 0$ configurations, and MbO₂ has dominant contributions from $s = 1$, with higher spin contributions at $s = 1.5$. This is consistent with our general observation that MbO₂ has larger valence fluctuations (entanglement in the ground-state) than MbCO.

Having shown how the Hund's coupling affects the orbital occupancy of the Fe site in Mb, and the associated charge transfer to the O₂ molecule, we investigate, in what follows, how the energetics of ligand binding to Mb are determined by these effects, and how the protein uses quantum fluctuations

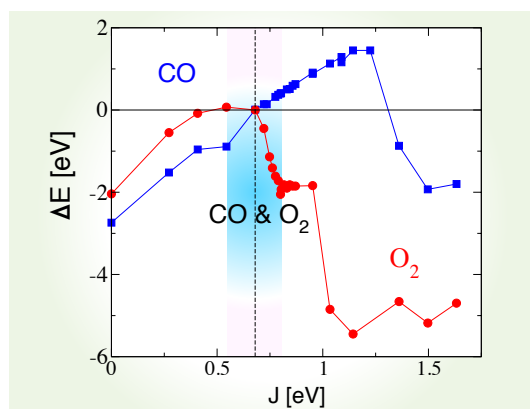


Fig. 5. Binding energetics: Hund's exchange coupling J -dependence of the DFT+DMFT total-energy of MbCO (blue) and MbO₂ (red), where the DFT energy of the diatomic ligand, CO or O₂, has been subtracted to give ΔE . A global arbitrary constant shift of the energy has been applied for clarity. The difference of binding energies $\Delta\Delta E$ is obtained by $\Delta\Delta E = \Delta E(\text{O}_2) - \Delta E(\text{CO})$. The physical regime, where $\Delta\Delta E$ is small, is shaded.

to discriminate between O₂ and CO. Fig. 2 shows the binding energies of O₂ and CO to Mb (to within a constant shift), calculated using DFT+DMFT, as a function of the Hund's exchange coupling J . At $J = 0$ eV, the binding energy of MbCO is approximately 1 eV more favorable than the binding energy of MbO₂, yielding an unphysical energetic imbalance. For $J > 0.7$ eV, we find, on the contrary, that the binding energy of MbO₂ is dramatically reduced. We attribute this to the enhancement of the spin magnetic moment in the Fe atom. In the intermediate regime, close to $J = 0.7$ eV, we find that the imbalance between MbO₂ and MbCO is thereby also dramatically reduced. In fact, the experimental binding free energy difference, between the two ligands, of 1.9 kcal/mol, is recovered from our calculations when J is near 0.7 eV, a typical value used for iron-based materials [32]. In this case, the effect of J on the binding energy of O₂ may be regarded as a balance between two competing effects. The charge analysis (Fig.2) reveals that metal-to-ligand charge transfer is higher for $J = 0$ eV, which is expected to enhance ligand-protein interactions for small values of J . However, NBO analysis reveals a larger ligand-to-metal back charge transfer for $J = 0.7$ eV, which is consistent with the increased occupancy of the Fe $d_{3z^2-r^2}$ orbital (Table 2), and is expected to cause variational energetic lowering at higher values of J due to electronic delocalization.

Compared to previously reported DFT studies, including our own DFT+ U study of the same system [13], the present study predicts a significantly larger charge on the O₂ molecule (-1.1 e versus -0.5 e). This charge is expected to stabilize the O₂ molecule in the Mb protein *via* hydrogen bond interactions with His64. Hence, we propose that both dynamical and multi-reference quantum effects, and large system sizes, must be accounted for in order to correctly determine the energetics of ligand binding in proteins with strongly correlated subspaces.

Conclusions

We have presented the application of a newly-developed methodology, designed to treat strong electronic interaction and multi-reference effects in systems of relatively very large numbers of atoms, to a molecule of important biological function. In particular, we have found that the Hund's coupling J is the crucial ingredient necessary to increase the multi-reference high-spin character of the ground-state, and so to bring the binding energetics into qualitative agreement with experiment. This provides a route to the solution of a long-standing problem in the density-functional theory based simulation of heme proteins, which often underestimates the Hund's coupling and incorrectly-describes multi-reference effects, namely an unphysically large imbalance of CO and O₂ binding energies. Our many-body description of the ligated myoglobin ground-state is further supported by quantitative agreement with experimental findings on both the ligand-dependence of the optical absorption spectra and the nature of the π -bonding in Fe-O₂. Our approach, optimized to describe molecules and nano-particles involving transition metal ions, supports a large range of applications, e.g., to strongly correlated oxide nano-particles [33] or to enzymes [34].

Methodology

In this work, we have carried out a detailed theoretical study of the electronic structure of the myoglobin molecule by means of a combination [22, 18] of linear-scaling density-functional theory (DFT) and the dynamical mean-field theory approximation (DFT+DMFT) [20, 35], a model which treats subspace-local dynamical, finite-temperature and

multi-determinantal effects, for given Hamiltonian parameters.

The ONETEP linear-scaling DFT code [21, 18, 37] was used to obtain the DFT ground-state. The ONETEP method is particularly advanced in terms of its accuracy, equivalent to that of a plane-wave method, which is arrived at by means of an *in situ* variational optimization of the expansion coefficients of a minimal set of spatially-truncated Nonorthogonal Generalized Wannier Functions [38] (NGWFs), and is based on direct minimization of the total-energy with respect to the single-particle density-matrix. The use of a minimal, optimized Wannier function representation of the density-matrix allows for the DFT ground state to be solved with relative ease in large systems, particularly in molecules where their explicit truncation implies that the addition of vacuum does not increase the computational cost.

Preparation of the structures for DFT+DMFT analysis have been described in detail elsewhere [13]. Briefly, the computational models are based on the X-ray crystal structures of sperm whale Mb in oxygenated and carbonmonxygenated ligation states (PDB: 1A6M, 1A6G) [9]. The heme group, ligand and 53 closest residues (1007 atoms in total) were extracted from the MbO₂ crystal structure and optimized using spin-polarized DFT, with the PBE [39] gradient-corrected exchange-correlation functional augmented by damped London potentials to describe van der Waals interactions [36]. Following optimization, the heme group and three closest residues were replaced by their positions in the MbCO crystal structure and re-optimized. This scheme ensures that energy differences are directly attributable to local changes in the binding site, while accounting for long-ranged polarization and constraints of the protein scaffold. The DFT binding energy was converged to better than 0.02 eV with respect to changes in the plane-wave energy cutoff and NGWF cutoff radii, and no additional restrictions on the variational freedom, such as the density kernel truncation, were invoked.

We refined our DFT calculations using the DFT+DMFT method [20, 35] in order to obtain a more accurate treatment of strong electronic correlation effects. In particular, DMFT introduces both quantum and thermal fluctuations, which are multi-reference effects not captured at the level of the Kohn-Sham DFT. In this, the Mb molecule was mapped, within DMFT, to an Anderson impurity model (AIM) Hamiltonian [40], and we used a recently developed extended Lanczos solver [41] to obtain the DMFT self energy. Since only a single impurity site (3d orbital subspace) is present, the system becomes crystal momentum independent in the molecular limit, and since the Kohn-Sham Green's function is computed in full, by inversion, before projection onto the impurity subspace, the Anderson impurity mapping is effectively exact, and the necessity of invoking the DMFT self-consistency is not required. However, in DFT+DMFT there is also a charge self-consistency cycle, albeit not routinely invoked at present due to computational cost, where the DFT+DMFT density kernel is used to generate a new Kohn-Sham Hamiltonian, which in turn provides a new input to the DMFT; the procedure being repeated until convergence is achieved. In this work, our data are obtained in the absence of charge self-consistency, however we checked that the corrections are small. Indeed, for MbO₂ at $J = 0.7$ eV, the changes obtained by converging the charge self-consistent DFT+DMFT induce a change in the energy of $\Delta E = -0.09$ eV, which corresponds to the energy of MbO₂ at $J = 0.72$ eV when the charge self-consistency is absent. Other changes are also small, for example, the chemical potential changes by +0.023 eV, and we find a change in the Fe

charge of +0.007 e. All these variations are consistent with a renormalized J (J increased by 3% at $J = 0.7$ eV).

To obtain the Kohn-Sham Green's function, we performed the matrix inversion, as well as all matrix multiplications involved in the DMFT algorithm, on graphical computational units (GPUs) using a tailor-made parallel implementation of the Cholesky decomposition written in the CUDA programming language.

Electronic correlation effects are described within the localized subspace by the Slater-Kanamori form of the Anderson impurity Hamiltonian [42, 43], specifically:

$$\mathcal{H}_U = U \sum_m n_{m\uparrow} n_{m\downarrow} + \left(U' - \frac{J}{2} \right) \sum_{m>m'} n_m n_{m'} \quad [1]$$

$$- J \sum_{m>m'} \left(2\mathbf{S}_m \mathbf{S}_{m'} + \left(d_{m\uparrow}^\dagger d_{m\downarrow}^\dagger d_{m'\uparrow} d_{m'\downarrow} \right) \right),$$

where m, m' are orbital indices, $d_{m\sigma}$ ($d_{m\sigma}^\dagger$) annihilates (creates) an electron with spin σ in the orbital m , n_m is the orbital occupation operator. The first term describes the effect of intra-orbital Coulomb repulsion, parametrized by U , and the second term describes the inter-orbital repulsion, proportional to U' , which is renormalized by the Hund's exchange coupling parameter J in order to ensure a fully rotationally invariant Hamiltonian (for further information on this topic, we refer the reader to Ref. [44]). The third term is the Hund's rule exchange coupling, described by a spin exchange coupling of amplitude J . \mathbf{S}_m denotes the spin corresponding to orbital m , so that $\mathbf{S}_m = \frac{1}{2} d_{ms}^\dagger \vec{\sigma}_{ss'} d_{ms'}$, where $\vec{\sigma}$ is the vector of Pauli matrices indexed by s and s' . In this work, we used $U = 4$ eV for the screened Coulomb interaction [16], and we explored the dependence of several observables on the Hund's coupling (in the range $J = 0 - 1.5$ eV). Our DMFT calculations were carried out at room temperature, $T = 293$ K. In this work, we used the canonical form of the double-counting potential V_{dc} , given by:

$$V_{dc} = U^{\text{av}} \left(n_d - \frac{1}{2} \right) - \frac{J}{2} (n_d - 1), \quad [2]$$

assuming paramagnetic occupancy $n_d = 2n_{d\sigma}$ of the d orbitals. Here, the parameter U^{av} is the intra- and inter-orbital averaged repulsion [45]. In our calculations we found that the DMFT solution remains paramagnetic, although the possibility of spontaneous formation of a magnetic moment (spin symmetry broken state) was allowed for. However, the low energy states are in a quantum superposition of polarized states, giving a fluctuating magnetic moment at the iron site. The theoretical optical absorption was obtained in DFT+DMFT within the linear-response regime (Kubo formalism), in the *no-vertex-corrections* approximation [46], where it is given by:

$$\sigma(\omega) = \frac{2\pi e^2 \hbar}{\Omega} \int d\omega' \frac{f(\omega' - \omega) - f(\omega')}{\omega} \quad [3]$$

$$\times \left(\rho^{\alpha\beta}(\omega' - \omega) \mathbf{v}_{\beta\gamma} \rho^{\gamma\delta}(\omega') \cdot \mathbf{v}_{\delta\alpha} \right),$$

and the factor of two accounts for spin-degeneracy, Ω is the simulation-cell volume, e is the electron charge, \hbar is the reduced Planck constant, $f(\omega)$ is the Fermi-Dirac distribution, and $\rho^{\alpha\beta}$ is the density-matrix given by the frequency-integral of the interacting DFT+DMFT Green's function. The matrix elements of the velocity operator, $\mathbf{v}_{\alpha\beta}$, noting that we do not invoke the Peierls substitution [46], are given by:

$$\mathbf{v}_{\alpha\beta} = -\frac{i\hbar}{m_e} \langle \phi_\alpha | \nabla | \phi_\beta \rangle + \frac{i}{\hbar} \langle \phi_\alpha | [\hat{V}_{nl}, \mathbf{r}] | \phi_\beta \rangle. \quad [4]$$

This expression is general to the NGWF representation [47], used in this work, where the contribution to the non-interacting Hamiltonian due to the non-local part of the norm-conserving pseudopotentials [48, 49], represented by \hat{V}_{nl} , is included. Once the self energy matrix is obtained, it can be used to correct the DFT total energy with the DMFT correction [50, 51]:

$$E = E_{DFT}[\hat{\rho}] - \sum'_{\mathbf{k}\nu} \epsilon_{\mathbf{k}\nu} + \text{Tr} [\hat{H}_{DFT} \hat{G}] + \langle \hat{H}_U \rangle - E_{DC}, \quad [5]$$

where \hat{H}_U indicates the many body interaction vertex of the DMFT, and the primed sum is over the occupied states. The symbol “Tr” indicates the one-electron trace for a generic representation and the sum over the Matsubara frequencies $i\omega_n$ of the finite-temperature many-body formalism. The interaction term \hat{H}_U is obtained with the Galitskii-Migdal formula [52]:

$$\langle \hat{H}_U \rangle = \frac{1}{2} \text{Tr} [\hat{\Sigma} \hat{G}], \quad [6]$$

$\hat{\Sigma}(\hat{G})$ is the self-energy (Green’s function) matrix in the NGWF representation. We note that both the self energy and the Green’s function are slowly decaying functions, hence the trace over Matsubara frequencies has to be done with care [50, 51]. Finally, the double-counting correction E_{DC} must be introduced, since the contribution of interactions between the correlated orbitals to the total energy is already partially included in the exchange-correlation potential derived from DFT. The most commonly used form of the double-counting term is [45]:

$$E_{dc} = \frac{U^{\text{av}}}{2} n_d (n_d - 1) - \frac{J}{2} \sum_{\sigma} n_{d\sigma} (n_{d\sigma} - 1). \quad [7]$$

A new approach, developed in this work, is the generation of natural bond orbitals based on the many-body Green’s function provided by DFT+DMFT, in order to obtain greater chemical insight into the ligand binding process. Natural bond orbitals (NBOs) [29] are post-processed linear-combinations of

the basis functions in which the density-matrix is expanded, such that the projection of the density-matrix onto the subspace formed by atom-based and atom-pair based subsets of basis-functions is maximally diagonal. In the current calculations the basis-functions in question are NGWFs [38], transformed to NBOs using the *NBO 5* programme [30], recently interfaced to ONETEP, as described in Ref. [31]. This procedure is carried out in such a manner that the final NBOs are then categorized into largely-occupied bonding and lone-pair orbitals, and largely-vacant anti-bonding and Rydberg orbitals. While normally applied to Kohn-Sham density-functional theory, to date, the NBO generation procedure is independent of the model (and so the Hamiltonian and self-energy) generating the density-matrix, and so we may apply it to the density-matrix integrated from the DFT+DMFT full Green’s function, for the first time. The resulting many-body NBOs largely retain the familiar profile of DFT-based NBOs, in this study, but their occupancies may be expected to deviate further from integer values due to quantum-mechanical and finite-temperature multi-reference effects captured within DFT+DMFT.

We computed the energy of MbCO and MbO₂ as a function of the Hund’s exchange coupling J . Defining $\Delta E_{CO} = E_{MbCO} - E_{CO}$ and $\Delta E_{O_2} = E_{MbO_2} - E_{O_2}$, the binding energy difference $\Delta\Delta E$ is given by $\Delta\Delta E = \Delta E_{O_2} - \Delta E_{CO}$. When $\Delta E_{CO} = \Delta E_{O_2}$, the MbO₂ and MbCO binding energies are identical. In comparisons with the experimental relative free energy of binding, we have assumed that the relative change in entropy of the two ligands upon binding is zero, which is a reasonable approximation for two sterically similar diatomic ligands.

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